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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/671,040	09/25/2003	Noel J. de Souza	U 014826-4	6697
140	7590	07/08/2004	EXAMINER	
LADAS & PARRY 26 WEST 61ST STREET NEW YORK, NY 10023			HUANG, EVELYN MEI	
			ART UNIT	PAPER NUMBER
			1625	

DATE MAILED: 07/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/671,040	<b>Applicant(s)</b> DE SOUZA ET AL.	
	<b>Examiner</b> Evelyn Huang	<b>Art Unit</b> 1625	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-7,22-26,33,38 and 43-46 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-7,22-26,33,38 and 43-46 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |  |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)            |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date ____ | 6) <input type="checkbox"/> Other: ____  |

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### DETAILED ACTION

1. Claims 1-7, 22-26, 33, 38, 43-46 are pending. Claims 8-21, 27-32, 34-37, 39-42 have been canceled according to the preliminary amendment filed on 9-25-2003.

#### *Claim Rejections - 35 USC § 102(e)*

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –  
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4-7, 38, 43, 44, 46 are rejected under 35 U.S.C. 102(e) as being anticipated by De Souza I (6514986).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention “by another,” or by an appropriate showing under 37 CFR 1.131.

The compounds of Formula I (column 4) as shown in Examples 1-5, the composition, method of use and process of making thereof (columns 8-10, Examples 1-5; columns 11-14, claims 1-30) are encompassed by the instant claims. While the above reference does not specify whether the arginine salt is D or L or is a racemate DL as in the instant claims, it is well known in the art that these are the only 3 possible forms for arginine. The public is therefore in possession of all these forms. The melting point and  $[\alpha]_D^{25}$  recited in the instant claims 22, 24 are physical properties intrinsic to the compound.

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***Claim Rejections - 35 USC § 102(e)***

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4-7, 38, 43, 44, 46 are rejected under 35 U.S.C. 102(e) as being anticipated by Patel I (2003/0207908, having the application number 09/566875, the US equivalent of WO 00/68229, PTO-1449) or Patel II (6750224, a CIP of 09/566875).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention “by another,” or by an appropriate showing under 37 CFR 1.131.

The compounds of Examples 7-8, the composition, method of use and process of making thereof (Patel I, page 15; page 25, claim 6, last two compound; Patel II, columns 27-28) are encompassed by the instant claims. While the above reference does not specify whether the arginine salt is D or L or is a racemate DL as in the instant claims, it is well known in the art that these are the only 3 possible forms for arginine. The public is therefore in possession of all these forms. The melting point and  $[\alpha]_D^{25}$  recited in the instant claims 22, 24 are physical properties intrinsic to the compound.

***Claim Rejections - 35 USC § 102(a)***

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 4-7, 38, 43, 44, 46 are rejected under 35 U.S.C. 102(a) as being anticipated by De Souza (WO 01/85095, PTO-1449). The compounds of Examples 1-5, the composition, the method of use and the process of making thereof (pages 13-16) are encompassed by the instant claims. While the above reference does not specify whether the arginine salt is D or L or is a racemate DL as in the instant claims, it is well known in the art that these are the only 3 possible forms for arginine. The public is therefore in possession of all these forms. The melting point and  $[\alpha]_D^{25}$  recited in the instant claims 22, 24 are physical properties intrinsic to the compound.

***Claim Rejections - 35 USC § 102(b)***

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4-6, 38, 43, 44, 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Patel III (WO 00/68229, PTO-1449). The antibacterial compound of Example 7 or 8 (pages 43-44), the composition, method of use, and the process of making thereof are encompassed by the instant claims. While the above reference does not specify whether the arginine salt is D or L or is a racemate DL as in the instant claims, it is well known in the art that these are the only 3 possible forms for arginine. The public is therefore in possession of all these forms. The melting point and  $[\alpha]_D^{25}$  recited in the instant claims 22, 24 are physical properties intrinsic to the compound.

***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 1-7, 21-26, 33, 38, 43-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishikawa (4399134, PTO-1449) or Hashimoto (PTO-1449) or Morita (PTO-1449) or Kido (PTO-1449) in view of Berge and/or Fujisawa (3984403, PTO-1449) and further in view of Kwan (5200558, PTO-1449).

Ishikawa generically discloses an antibacterial piperidiny1-benzoquinolizine compound or a pharmaceutically acceptable salt thereof, its composition and method of use (columns 2-3). Specific compounds, including nadifloxacin, are described (column 54, claims 20, 21; column 21, lines 1-10). (S)-(-)-Nadifloxacin is expressly taught by Hashimoto and Morita. Indeed, (S)-(-) Nadifloxacin is known to be 60-250 times more potent than the (+) isomer, and its synthesis has been described (Hashimoto, page 642, paragraph 1; Morita, page 245).

Ishikawa, Morita or Hashimoto does not teach the hydrates of the Nadifloxacin as in the instant claims. However, Kido expressly teaches that different crystal structures exist for Nadifloxacin dependent on the solvent used for recrystallization (page 872, second paragraph). More specifically, anhydride is obtained from acetonitrile whereas hemihydrate is obtained from aqueous ethanol (page 872, third paragraph).

Guided by the teaching of Kido, one of ordinary skill in the art would be motivated to prepare the hydrates of Ishikawa's compound having various amount of water by using different solvents for recrystallization as taught by Kido to arrive at the instant invention.

While Ishikawa generically teaches that the benzoquinolizine compound may be in the form of a pharmaceutically acceptable salt, he does not teach the instant arginine salt. Berge, generally teaches that amino acids, such as arginine, have been used as salt forming agent for reduction of toxicity of the drug (page 3, column 2, second paragraph). Arginine salts of certain

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antibacterial compounds have been shown to lower the toxicity, improve stability and modify the hygroscopicity of the parent drug compound (page 5, Table III). Fujisawa specifically teaches that arginine salt of the antibacterial cephalosporin has the advantages of being more stable, more soluble, and causing substantially no pain upon parenteral application (column 1, lines 5-30). Guided by the teaching of Berge and Fujisawa, one of ordinary skill in the art would be motivated to prepare the arginine salt of the piperidinyl-benzoquinolizine compound of Ishikawa to arrive at the instant invention with the reasonable expectation of reducing the toxicity while improving stability of the parent drug compound.

While the above references does not specify whether the arginine salt is D or L or is a racemate DL as in the instant claims, it is well known in the art that these are the only 3 possible forms for arginine. The public is therefore in possession of all these forms. While the L-arginine is the naturally occurring form, the D-arginine and DL acid are also commercially available. Furthermore, Kwan has shown that both the D or the L arginine salt of a drug give an onset-hastened, enhanced response (column 1, lines 40-50).

At the time of the invention, guided by the combined teachings of the prior art, one of ordinary skill in the art would be motivated to prepare the D or L or DL arginine salt of the piperidinyl-benzoquinolizine compound of Ishikawa to arrive at the instant invention with the reasonable expectation of obtaining an antibacterial compound with enhanced activity.

8. Claims 1-7, 22-26, 33, 38, 43-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patel III (WO 00/68229, PTO-1449) in view of Kwan (5200558, PTO-1449).

Patel generically teaches the S-(-) piperidinyl-benzo[I, l]quinolizine carboxylic acid, or the pharmaceutically acceptable salts, hydrates, polymorphs thereof. The L-arginine salt is exemplified on pages 43-44, Examples 7, 8.

While Patel does not specify that the arginine salt is D or L or is a racemate DL and only the L-arginine salt is exemplified, it is well known in the art that these are the only 3 possible forms for arginine. The public is therefore in possession of all these forms. The D-arginine and DL acid are also commercially available. Furthermore, Kwan has shown that both the D or the L arginine salt of a drug give an onset-hastened, enhanced response (column 1, lines 40-50). The melting points recited in the instant claims are intrinsic properties of the compounds.

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At the time of the invention, guided by the combined teachings of the prior art, one of ordinary skill in the art would be motivated to prepare the D or L or DL arginine salt of the piperidiny1-benzoquinolizine compound of Patel to arrive at the instant invention with the reasonable expectation of obtaining an antibacterial compound with enhanced activity.

### ***Double Patenting***

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-7, 22-26, 38, 43-46 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of copending Application No. 09/566875 (US 2003/0207908, the US equivalent of WO 00/68229), or over claims 1-28 of copending Application No. 09/566875 (US 2003/0207908, the US equivalent of WO 00/68229) in view of Kwan for reasons set forth in paragraphs 3, 5 and 8 above.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 1, 2, 4-7, 22-26, 38, 43, 44, 46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-30 of U.S. Patent No.



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6514986. Although the conflicting claims are not identical, they are not patentably distinct from each other because of reasons set forth in paragraph 2 above.

12. Claims 1-7, 22-26, 33, 38, 43-46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6664267. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented compound, composition, method of use and process of making thereof, are encompassed by the instant claims.


### ***Conclusion***

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
Evelyn Huang  
Primary Examiner  
Art Unit 1625